REMARKS

Claims 1-6, 8-12, and 15-42 were pending in the application. Claims 1, 8, 9, 19, 20, and 32 have been amended and claims 7 and 13-14 were previously cancelled. Accordingly, claims 1-6 and 8-12 and 15-42 remain pending.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

As a preliminary matter, Applicant thanks the Examiner for her time and courtesy during the brief telephonic interview on July 23, 2009 during which the Examiner indicated that the Office Action incorrectly referred to a Schneider reference. No Schneider reference is being applied to the claims in the instant Office Action. The Examiner stated that the rejection was meant to be made in view of Yano.

Rejection of claims under 35 U.S.C. §112, second paragraph

The Office Action has rejected claims 1-6, 8-12, and 15-42 under 35 U.S.C. §112, ¶2 for allegedly being indefinite for including the expression "at least about." Applicant respectfully disagrees. However, purely to progress the prosecution of the instant application, applicant has amended the claims as set forth above to remove the expression "at least" from the claims. Withdrawal of the rejection is respectfully requested.

Rejection of Claims under 35 U.S.C. §103(a)

The Office Action has rejected claims 1-6, 8-12, and 15-42 under 35 U.S.C. §103(a) as allegedly being unpatentable over Ueno (US Patent 6,566,398) and Yano et al. (J. Nutrition. 130:1095-1101, 2000) in view of Troyer et al. (US Patent 6,506,412) and Schneider et al. (in error). Applicant respectfully disagrees.

The Office Action asserts that "Ueno teaches the use of n-6 fatty acids containing oil and N-3 fatty acids containing oil such as DHA and EPA in a pharmaceutical formulation for the treatment of dry eye or dry mouth syndrome. See the abstract, column 4, lines 9-40" (bottom of page 3 of the Office Action)

Applicant submits that the abstract teaches "administering ***a fatty acid derivative***" (emphasis added). Each DHA and EPA are fatty acids, not fatty acid derivatives.

Further, in column 4, lines 9-40 referred to in the Office Action, again teaches the administration of ***a fatty acid derivative*** (lines 15-16) and provides an essentially infinite number of compounds that can be used in the method of the invention. For example, the compounds listed in claim 1 provide over 150,000 possible compounds. The list provided in the section of column 4 pointed to in the Office Action is likely even larger.

The issue of obviousness in chemical cases has been reviewed by the Courts in view of the recent *KSR* decision.

> "While the *KSR* Court rejected a rigid application of the . . . TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying '***a reason*** that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination."
>
> "When there is a design need or market pressure to solve a problem and there is a ***finite number of identified, predictable solutions***, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. ***Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.*** Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound." *Takeda Chemical Industries Ltd. v. Alphapharm Pty*. 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The Ueno reference provides a number of successful experiments using ***a single fatty acid derivative*** -- 13,14-dihydro-15-keto-16,16-difluoro-PGE[1] (see each of the examples). In each example, Ueno concludes that the compound, administered at a very low dose, typically as a topical 0.001% or 0.0001% solution or at an oral dose of 1 mg/kg, provided the desired outcome, e.g., corrected dry eye, promoted salivation. Provided with these successful experiments, there is no design need or market pressure to make the new invention. Moreover, there is no teaching or suggestion in Ueno to use more than one fatty acid derivative at a time.

Further, as no problem is presented by Ueno, and an essentially infinite list of compounds is presented by Ueno, there is not a "***finite number of identified, predictable solutions***" provided by the reference as required by the *Takeda Chemical Industries Ltd. v. Alphapharm Pty* decision cited above. Instead, the cited reference provides "***a broad selection of compounds any one of which could have been selected as a lead compound for further investigation***" with no teaching or suggestion that the combination of disclosed compounds claimed would provide the benefits demonstrated in the Examples of the instant application (discussed below). The possible at least three-way combinations of over 150,000 compounds provided by Ueno, optionally including a fourth compound, at various dosage ranges, to arrive at the claimed invention cannot be considered to make the instantly claimed invention obvious or within the skill of the ordinary artisan.

Further Ueno provides a strong preference for prostaglandin compounds and ***fatty acid derivatives***, such as those provide in the claims, rather than naturally occurring fatty acids, such as those instantly claimed.

In Figure 1, Applicant provides a flow chart using the N-3 fatty acid pathway. Although EPA does breakdown to form DHA, different results are observed upon administration of a combination of the fatty acids, rather than a single fatty acid alone. Moreover, administration of a precursor of both EPA and DHA, e.g., α-linolenic acid, does not provide the same beneficial effects as administration of EPA and DHA as instantly claimed.

Moreover, it is a goal of Ueno to provide as low a dose as possible of the compound for treatment. In column 12, lines 33-51, the term "effective amount" is defined as being a dosage of about 0.000001-10% of the active agent, for topical or sublingual administration. Example 4 provides a dose of 1 mg/kg for oral administration (column 17, line 51). The importance of limiting the dose to limit any undesirable side effects is specifically taught by Ueno, for example in the paragraph bridging columns 3 and 4.

The instant claims are drawn to a dose of "about 150-550 mg of eicosapentaenoic acid (EPA) and about 50-500 mg docosahexaeonic acid (DHA)". That would provide a minimum dose of about 200 mg, plus the n-6 containing fatty acid. ***As the average adult is typically considered to be about 70 kg; therefore, the low end of the dosage range instantly claimed would be in excess of 3 mg/kg, far in excess of the amount taught by Ueno.***

Per section 2141.02(VI) MPEP, the prior art must be considered ***in its entirety***, including disclosures that teach away from the claims, e.g., the desirability of the use of ***low doses*** of the compounds, and the desirability of the use of ***fatty acid derivatives*** rather than naturally occurring fatty acids. Specifically, section 2141.02(VI) of the MPEP states:

> A prior art reference must be considered ***in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.*** *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, *i.e.*, that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.).

> However, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise ***discourage the solution claimed***.." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). [emphasis added]

Ueno clearly criticizes, discredits, and discourages the use of the high doses of compounds as claimed in the instant application. Ueno teaches that high doses result in undesirable side effects. ***The use of the lowest possible doses of the compounds is an essential aspect of the methods provided by Ueno.*** Moreover, the low doses of Ueno provide the desired effects without unwanted side effects. Provided with the teachings of Ueno, one of skill in the art would not consider using the relative high doses of fatty acids instantly claimed. Further, in the repeated teachings of the use of ***fatty acid derivatives***, Ueno discourages the use of the naturally occurring fatty acids claimed.

Although the *KSR* decision has eliminated the rigid application of the TSM test, the requirement for a motivation to combine the references is still required. As discussed in section 2143.01 of the MPEP:

> IV. *>MERE STATEMENT< THAT THE CLAIMED INVENTION IS WITHIN THE CAPABILITIES OF ONE OF ORDINARY SKILL IN THE ART IS NOT SUFFICIENT BY ITSELF TO ESTABLISH PRIMA FACIE OBVIOUSNESS
>
> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness ***without some objective reason to combine the teachings of the references***. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). **">[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, ***there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness***.'" *KSR,* 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).< [emphasis added]

V. THE PROPOSED MODIFICATION CANNOT RENDER THE PRIOR ART UNSATISFACTORY FOR ITS INTENDED PURPOSE

> If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

No objective reasoning can be provided to combine three less preferred compounds from the virtually infinite list of possible compounds provided by Ueno, and provide them at the ***relatively high doses claimed***, which is taught against by Ueno. There can be no rational underpinning to support the legal conclusion of obviousness based on the cited references. Therefore, the rejection cannot stand.

The assertion in the Office Action that "Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention" is incorrect and does not consider the Examples provided in the specification. In Example 2, a 68 year old woman with dry eyes found a substantial advantage in combining flaxseed oil, a rich source of γ-linolenic acid, with fish oil, a rich source of n-3 and n-6 fatty acids, particularly EPA and DHA, for treatment of dry eyes. ***This result demonstrates an advantage of the specifically claimed combination of fatty acids as compared to a single fatty acid***.

In Example 3, in a much larger population, subjects who consumed large amounts of tuna fish, which is rich in EPA and DHA, were found to have much lower incidence of dry eye than the study population as a whole. Importantly, the consumption of tuna was found to have a ***highly significant dose-response relationship*** with reduction of dry eye, suggesting a direct causal relationship between the quantity of tuna consumed and the decreased incidence of dry eye. These results are surprising and could not have been predicted based on the teachings of Ueno. Applicant notes that Ueno teaches γ-linolenic acid as a fatty acid in the same portions of the specification that Ueno teaches EPA and DHA (see, *e.g.* column 3, line 15 and column 4, line 29) and provides no suggestion that any one or more of the naturally occurring fatty acids should be selected over another. Although the claimed invention

further includes an n-6 rich oil, it does not diminish the demonstrated effect of DNA and EPA. Ueno provides no teaching or suggestion regarding the advantage of using one particular fatty acid over another, of the benefits of the combination of the instantly claimed fatty acids, that would allow one to arrive at the surprising results of the instant invention as demonstrated in the Examples.

The Office Action points to Yano to allegedly demonstrate that "the addition of vitamin E to DHA can exert beneficial effects on organ on organ [*sic*] dysfunction associated diseases. See abstract" (top of page 4 of the Office Action). Applicant submits that Yano teaches that the combination of compounds "might exert beneficial effects on organ dysfunction associated ***with various TNF-related diseases***" [see abstract, emphasis added] No reference cited teaches or suggests that any of the claimed conditions are TNF-related diseases. There are no teachings on Ueno or Troyer that dry eye or dry mouth can be a result of apoptosis.

Yano provides no teaching or suggestion that modulation of apoptosis could be useful for the treatment of dry eye or dry mouth. In fact, ***Yano questions the utility of modulating apoptosis under any circumstance***. Particularly, the first sentence of the last paragraph states "At the present time, it is unclear whether apoptosis induced by various stimuli is harmful or beneficial in various physiological and pathological circumstances." Therefore, based on the teachings of Yano as a whole, one could not be motivated to administer a composition for inhibiting apoptosis.

Moreover, as Yano is directed to experiments performed in tissue culture, the reference can provide no information in regard to dosages which is a claimed aspect of the instant invention. However, if one could glean information regarding dosages from tissue culture experiments, one would be disinclined to use high doses, such as those instantly claimed, as "DHA, EPA and AA exhibited cytotoxicity when these fatty acids were added to culture in high amounts compared with the BSA or serum protein level" (middle of column 1, page 1100).

Further, based on the teachings of Yano, one would not expect EPA to be useful for the inhibition of apoptosis. In the studies of Yano, EPA showed weak activity in inhibiting TNF induce apoptosis, and no activity in TNF and CHI induced apoptosis (paragraph bridging columns, page 1100). Yano concludes "Docosapentaenoic acid retained during the preincubation with EPA might be insufficient to reduce apoptosis induced with stronger stimulation."

Yano also teaches the disadvantages of the use of vitamin E. It was necessary to pre-incubate the cells for 24 hours to obtain a synergistic effect with DHA, whereas the use of water soluble anti-oxidants provided a much more rapid effect (first full paragraph, column 2, page 1100).

The Office Action points to Troyer (sometimes identified as Troy) to allegedly demonstrate "the use of omega 3-fatty acids and omega-6 fatty acids in a pharmaceutical formulation for the treatment of dry eye syndrome." Troyer claims such compositions which further require the inclusion of vitamin A, and optionally include a water soluble anti-oxidant. Yano is relied on to provide teachings regarding vitamin E.

Applicant submits that the rejection fails as none of the references teach the use of DHA and EPA with an n-6 rich oil and an ***oil soluble anti-oxidant***, e.g. vitamin E, in a formulation for the treatment of dry eye or mouth. Troyer teaches the use of ***water soluble anti-oxidants*** in formulas for the treatment of dry eye. Although Yano teaches the use of vitamin E as an agent to reduce apoptosis, Yano does not teach that apoptosis can be associated with dry eye or dry mouth, and teaches the limitations of the use of vitamin E.

Further, Applicant asserts that Troyer provides no teachings or suggestions regarding possible dosage ranges that overlap with the instantly claimed ranges.

In regard to dosing, the Office Action asserts that Troyer et al "teach the combination of omega-3 fatty acids, omega-6 fatty acids and GLA at least 94 mg." The Office Action asserts that the selection of dosage and relative proportions is within the

ability of one of skill in the art. The instantly claimed invention provides a dose of 200-1050 mg of fatty acids DHA and EPA, plus an n-6 fatty acid. This is over 2- to 10-fold excess of the cited reference.

Section 2144.05(II)(A) of the MPEP which relates to optimization within prior art conditions or through routine experimentation states:

> Generally, differences in concentration or temperature will not support the patentability of subject matter ***encompassed by the prior art*** unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

The instantly claimed ranges are not "encompassed by the prior art" and do not constitute "general conditions" provided in the cited art, but instead are substantially outside of the cited art by at least 2-fold up to greater than 10-fold. Both of the other cited references caution against dosing fatty acids in large amounts. Moreover, as discussed above, the specific combination of fatty acids claimed provides a surprising beneficial effect over the administration of other fatty acids, either alone or in combination with each other. As the claimed ranges are outside of those taught by the cited art, they cannot be obvious in view of the cited art.

The Office Action states that, "The references also make clear that Vitamin B12 has been previously used as an antioxidant in compositions for the treatment of dry eye." Vitamin B12 is a ***water soluble anti-oxidant***. The instant claims are directed to the use of an ***oil soluble anti-oxidant***. No evidence has been provided by the Examiner of the use of an oil soluble anti-oxidant, as claimed, in a formulation for the treatment of dry eye or dry mouth as instantly claimed. The use of an oil-soluble anti-oxidant for the inhibition of apoptosis cannot provide the support for the rejection.

None of the cited references, either alone or in combination with each other, provide teachings or suggestions, to provide the claimed combination of DHA and EPA and an n-6 fatty acid rich oil for the treatment of any of the claimed conditions.

Moreover, as the references teach successful methods for the treatment of dry eye syndrome, there can be no motivation to alter the methods to provide the methods and compositions instantly claimed herein.

Accordingly, Applicants respectfully request withdrawal of the rejection.

FEES AND REQUEST FOR EXTENSION IN TIME FOR REPLY

The Commissioner is hereby authorized to charge Deposit Account 04-1105 the fee for a three month extension in time for reply, small entity, referencing Docket No. 2022(200696). It is believed that no further fee is due with this response. However, if an additional fee is due, with this paper or any other paper filed by this Firm in relation to this case, the Commissioner is authorized to charge the Deposit Account listed above referencing the docket number provided. Credit of any overpayments is respectfully requested.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance. If a telephone conference would expedite allowance of this application, the Examiner is urged to call the undersigned.

Dated: October 14, 2009

Respectfully submitted,

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